and FR4), or FRs, to replace the corresponding FRs of the parent immunoglobulin. Free assortment of these FRs from different immunoglobulins and from different species can be mixed and matched into forming the final immunoglobulin chain. A set of criteria in the choice of these FRs to minimize or eliminate the need to re-introduce framework amino acids from the parent immunoglobulin for patching is described. The approach gives greater flexibility in the choice of framework sequences, minimizes the need to include parent framework amino acids, and most importantly, reduces the chances of creating new T- and B-cell epitopes in the resultant immunoglobulin. --

A1

In the claims

2. (Amended) A re-engineered, or FR-patched immunoglobulin according to claim 1, in which the particular FR chosen for patching or replacing each corresponding FR in the parent immunoglobulin:

a. exhibits the highest degree of homology, or at least 60%, to the corresponding parent FR;

b. exhibits identical sequence homology to the corresponding parent FR at the three amino acids immediately adjacent to the flanking CDR's; and

A2

c. contains identical amino acid to the corresponding parent FR at positions known to be close to, or have interactions with the CDR's/antigen binding site, as evaluated by computer modeling, crystal structure, published information, or prior experience.

4. (Amended) A re-engineered, or FR-patched immunoglobulin according to claim [()1()], in which the particular FR chosen for patching or replacing each corresponding FR in the parent immunoglobulin:

A3

a. exhibits the highest degree of homology, or at least 60%, to the corresponding parent FR;

b. exhibits the highest degree of sequence homology to the corresponding parent FR, preferably 100%, or contains conservatively similar amino acids, such as, gly, ala; val, ile, leu; asp, glu; asn, gln;

ser, thr; lys, arg; and phe, tyr, at the three amino acids immediately adjacent to the flanking CDR's; and

c. contains identical, or conservatively similar amino acids (as listed in claim 4b) to the corresponding parent FR at positions known to be close to, or have interactions with the CDR's/antigen binding site, as evaluated by computer modeling, crystal structure, published information, or prior experience.

5. (Amended) A re-engineered, or FR-patched immunoglobulin according to claim [(]1[)], in which the particular FR chosen for patching each corresponding FR in the parent immunoglobulin:

a. exhibits the highest degree of homology, or at least 60%, to the corresponding parent FR;

A3

b. exhibits the highest degree of sequence homology to the corresponding parent FR, preferably 100%, or contains conservatively similar amino acids (as listed in claim 4b) at the four amino acids immediately adjacent to the flanking CDR's; and

c. contains identical, or conservatively similar amino acids (as listed in claim 4b) to the corresponding parent FR at positions known to be close to, or have interactions with the CDR's/antigen binding site, as evaluated by computer modeling, crystal structure, published information, or prior experience.

6. (Amended) A re-engineered, or FR-patched immunoglobulin according to claim 1, 2, 3, 4 [and] or 5 containing the heavy and/or light chain variable region sequences from a parent antibody, in which the particular FR chosen for patching each corresponding FR in the parent immunoglobulin comprises re-introduced amino acids from

the parent immunoglobulin framework outside the Kabat and Chothia CDRs, wherein the back mutated amino acids replace corresponding amino acids in the patching FR , which is the particular FR derived from a different source used for patching, or that replaces the original FR of, the parent immunoglobulin, and each of said back mutated amino acids:

a. is adjacent to a CDR in the donor immunoglobulin sequence, or

b. contains an atom within a distance of 4 Å of a CDR in said re-engineered immunoglobulin.

7. (Amended) A re-engineered, or FR-patched immunoglobulin according to claim 1, 2, 3, 4 [and] or 5 containing the heavy and/or light chain variable region sequences from a parent antibody, in which the particular FR chosen for patching each corresponding FR in the parent immunoglobulin comprises re-introduced amino acids from the parent immunoglobulin framework outside the Kabat and Chothia CDRs, wherein the back mutated amino acids replace corresponding amino acids in the patching FR, which is the particular FR derived from a different source used for patching, or that replaces the original FR of, the parent immunoglobulin, and each of said back mutated amino acids:

a. is adjacent to a CDR in the donor immunoglobulin sequence, or

b. contains an atom within a distance of 5 Å of a CDR in said re-engineered immunoglobulin.

8. (Amended) A re-engineered, or FR-patched immunoglobulin according to claim 1, 2, 3, 4 [and] or 5 containing the heavy and/or light chain variable region sequences from a parent antibody, in which the particular FR chosen for

patching each corresponding FR in the parent immunoglobulin comprises re-introduced amino acids from the parent immunoglobulin framework outside the Kabat and Chothia CDRs, wherein the back mutated amino acids replace corresponding amino acids in the patching FR, which is the particular FR derived from a different source used for patching, or that replaces the original FR of, the parent immunoglobulin, and each of said back mutated amino acids:

a. is adjacent to a CDR in the donor immunoglobulin sequence, or

b. contains an atom within a distance of 6 Å of a CDR in said re-engineered immunoglobulin.

9. (Amended) A re-engineered, or FR-patched immunoglobulin according to claim 1, 2, 3, 4 [and] or 5 containing the heavy and/or light chain variable region sequences from a parent antibody, in which the particular FR chosen for patching each corresponding FR in the parent immunoglobulin comprises re-introduced amino acids from the parent immunoglobulin framework outside the Kabat and Chothia CDRs, wherein the back mutated amino acids replace corresponding amino acids in the patching FR, which is the particular FR derived from a different source used for patching, or that replaces the original FR of, the parent immunoglobulin, and each of said back mutated amino acids:

a. is adjacent to a CDR in the donor immunoglobulin sequence, or

b. is capable of interacting with amino acids in the CDRs, or

c. is typical at its position for the species of the particular FR chosen for the patching, and the replaced amino acid in the said FR is rare at its